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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/590,541 | 08/25/2006 | James R. Eshleman | 62310(71699) | 9774 |

49383 7590 12/24/2009

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| EXAMINER | |
|---|---|
| KAPUSHOC, STEPHEN THOMAS | |
| ART UNIT | PAPER NUMBER |
| 1634 | |
| MAIL DATE | DELIVERY MODE |
| 12/24/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/590,541 | ESHLEMAN ET AL. | |
| | Examiner | Art Unit | |
| | STEPHEN KAPUSHOC | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,10-13,23,28-30,40-42 and 75-83* is/are pending in the application.

4a) Of the above claim(s) *1-5,23,28-30,40-42,75 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,10-13 and 77-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-6, 10-13, 23, 28-30, 40-42, and 75-83 are pending.

Claims 1-5, 23, 28-30, 40-42, 75 and 76 are withdrawn from examination as detailed in the Office Action of 12/16/2008.

Claims 6, 10-13 and 77-83 are examined on the merits.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/07/2009 has been entered.

This Office Action is in reply to Applicants' correspondence of 10/07/2009.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Election/Restrictions*

1. It is noted that Applicants have elected for the examination of claims as they require the particular KRAS2 mutation that is G35A, where the instant claims encompass non-elected subcombinations in the recitation "at least one of a G35A, a G35T, or a G34C". No claim is indicated as allowed in this Office Action. Prior to the allowance of the application any non-elected subject matter which has not been rejoined with the elected subject matter will be required to be deleted from the claims.

***Withdrawn Claim Rejections - 35 USC § 112 1st ¶ Written Description, New Matter***

2. The rejection of claims under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for containing new matter, as set forth on pages 2-3 of the Office Action of 07/07/2009, is **WITHDRAWN** in light of the amendments to the claims.

***New Claim Objections***

3. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case claim 10 requires "determining the KRAS mutation level", but this limitation is redundant with the limitations of claim 6, from which claim 10 depends, where claim 6 requires a step "to determine a mutation level".

4. Claim 6 objected to because of the following informalities: Claim 6 recites the clause:

> wherein detecting a nucleotide difference in KRAS2 wherein the nucleotide difference comprises at least one of a G35A, a G35T, or a G34C nucleotide substitution in the nucleic acid of the subject differentiates pancreatic cancer from pancreatitis

where the phrase with commas separating the second wherein clause, as shown below, is correct

> wherein detecting a nucleotide difference in KRAS2, wherein the nucleotide difference comprises at least one of a G35A, a G35T, or a G34C nucleotide substitution, in the nucleic acid of the subject differentiates pancreatic cancer from pancreatitis

Appropriate correction is required.

***Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement Maintained in Part***

5. Claims 6, 10-13 and 77-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

> A method of differentiating pancreatic cancer from chronic pancreatitis in a human subject, said method comprising:
> obtaining a biological sample from said human subject, said sample comprising nucleic acids from said subject;
> hybridizing said nucleic acids with at least one oligonucleotide pair to form a reaction mixture; wherein said oligonucleotide pair comprises a first oligonucleotide and a second oligonucleotide; wherein said first oligonucleotide comprises a first gene specific region and a first primer region, and said second oligonucleotide comprises a second gene specific region and a second primer region; wherein either said first oligonucleotide or said second oligonucleotide specifically hybridizes to the nucleotide sequence encoding the A allele of the G35A nucleotide mutation in the KRAS2 gene, said G35A nucleotide mutation encoding the G12D KRAS2 amino acid substitution; and wherein said first oligonucleotide said second oligonucleotide are suitable for ligation to one another;
> subjecting the reaction mixture to a ligation reaction to form a ligation product;
> amplifying said ligation product to form a reaction product;

> detecting said reaction product, wherein detecting said reaction product indicates the presence of said A allele of the G35A nucleotide mutation in the KRAS2 gene in said nucleic acids from said subject;
>
> wherein the presence of said A allele of the G35A nucleotide mutation in the KRAS2 gene in said nucleic acids from said subject is indicative of an increased likelihood of the presence of pancreatic cancer in said subject.

does not reasonably provide enablement for the breadth of the method as claimed which encompasses analysis of samples in any subject organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

**Nature of the invention and breadth of the claims**

The claims are drawn to methods of differentiating pancreatic cancer from chronic pancreatitis using a particular amplification methodology to detect nucleotide content.

The claims encompass the analysis of any subject organism.

The invention thus requires knowledge of a correlative association between a G35A nucleotide substitution in the KRAS2 gene in any organism and the presence of either pancreatic cancer or chronic pancreatitis.

**Direction provided by the specification and working example**

The instant specification provides examples (e.g. pages 76-91) of the analysis of KRAS2 mutations in human patients with either pancreatic cancer on non-cancerous pancreatic disorders. The specification provides, consonant with the election, the analysis of (see for example p.12 p.89) a specific KRAS2 gene mutation identified as G35A (a G to A mutation at position 35, where the A of the initiator ATG is position 1)

which changes codon 12 from GGT to GAT, changing amino acid 12 from glycine to aspartic acid (this nucleotide mutation is known in the art as the G12D mutation). The specification provides that the presence of the G12D encoding mutation is indicative of pancreatic cancer as opposed to benign disease (for example Table 4, p.91).

The specification does not provide for any analysis of any non-human subjects.

**State of the art, level of skill in the art, and level of unpredictability**

While the state of the art and level of skill in the art in detecting variable nucleotide content at any known mutation hot spot is high, the unpredictability in extrapolating variable nucleotide content from any one organism to any other different organism is higher. The high level of unpredictability is demonstrated by the prior art.

It is relevant to point out the unpredictability in extrapolating the presence of polymorphic nucleotide content, or its association with any phenotype, form one animal to any other different animal. Such unpredictability in interspecies extrapolation is addressed by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

**Quantity of experimentation required**

A large and prohibitive amount of experimentation would be required to make and use the claimed invention in the full scope of the claims. Within the scope of the claimed invention one would have to perform experimentation in any non-human subjects whether or not nucleic acid content is particularly indicative of either pancreatic cancer or chronic pancreatitis. Even if one were to perform such experimentation, there

is no assurance that any other reliable associations, beyond those identified earlier in this rejection (i.e.: the association of G35A with cancer in humans) as enabled by the instant specification would be found.

**Conclusion**

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the specific working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the claimed invention in the full scope as encompassed by the claims.

**Response to Remarks**

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement in the full scope encompassed by the claims. Applicants' arguments (p.9 of the Remarks) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection. Applicants have argued that the claims are amended to recite a G35A nucleotide substitution, however as set forth in the rejection the claims encompass any subject organisms but the specification is enableing only for the analysis of human subjects.

The rejection as set forth is **MAINTAINED.**

***Maintained Claim Rejections - 35 USC § 103***
***Newly applied to claims as necessitated by amendments***

6. Claims 6, 10-13 and 77-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schouten et al (2002), as cited on the IDS of 08/25/2006, in view of Maire et al (2002) and Lecomte (2002).

With regard to the limitations of claim 6, Schouten et al (summarized in Fig.2 on p.4, and Fig 8 on p.11) teaches a method that comprises contacting a nucleic acid sample with a pair of oligonucleotides in which each of the oligonucleotides has a gene specific region (termed 'hybridisation sequence' in the reference) and a primer region (termed 'PCR primer sequence Y' and 'PCR primer sequence X' in the reference). The reference indicates that mutation detection can be accomplished by using a nucleotide difference (as compared to the target nucleic acid sequence) in the gene specific region of one oligonucleotide (p.11, right col., lns.5-10). The method steps of the reference indicate that the primers of the pair are suitable for ligation to one another (p.2, right col., ln.1). Furthermore the reference teaches a ligation reaction and amplification of the formed ligation product (p.2, right col., ln.1-23). The reference teaches analyzing the reaction product (Fig 3).

Regarding claims 80 and 81, Schouten et al teaches that primers contain a stuffer sequence of varying length (Fig 2), where a stuffer sequence is a foreign DNA region between the gene specific sequence and the primer region (relevant to claim 80), and allows detection of the particular amplicon (e.g. Fig 8 legend) thus acting as a probe (relevant to claim 81).

Schouten et al does not specify the analysis of a G35A KRAS mutation, nor that a G35A KRAS mutation is indicative of a phenotype.

However, the analysis of a G35A mutation in KRAS2 and its association with pancreatic cancer was well known in the art at the time the invention was made.

Maire et al teaches the analysis of mutations in differentiating between pancreatic cancer and chronic pancreatitis.

Relevant to claims 6, 10, and 13, Maire et al teaches the analysis of G12D mutations in codon 12 of the KRAS2 gene (p.552 – Detection of KRAS2 gene mutations). Relevant to the limitations of claim 6, the mutation analyzed by the allele specific amplification of Maire et al is the same G35A mutation of the instant specification, as evidenced by Lecomte et al (Table 1). Relevant to claims 10 and 13, the analysis of allele specific amplification products is determining a KRAS mutation level (relevant to claim 10) and analysis of mutations in subjects is monitoring KRAS mutation levels (relevant to claim 13).

Relevant to the limitations of claims 11 and 12, Maire et al teaches that the presence of the KRAS2 G35A mutation is indicative of pancreatic cancer as opposed to chronic pancreatitis (p.552 – KRAS2 mutations in circulating DNA; p.551 - Abstract). With regard to the limitations of claims 11 and 12, the teachings of Maire et al indicate that a mutation level of 0.0% (e.g. undetected KRAS2 mutation) is indicative of chronic pancreatitis (claim 11), and a mutation level of 100% (e.g. KRAS2 mutation detected in all samples from a subject) is indicative of pancreatic cancer (claim 12).

Relevant to the limitations of claims 77-79, Maire et al teaches that methods comprising KRAS2 mutation analysis can have 98% sensitivity, which meets the limitations of claims 77-79.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Schouten et al for the analysis of the KRAS2 G12D mutation as taught by Maire et al to be indicative of the presence of pancreatic cancer. One would have been motivated to analyze the mutation of Maire et al based on the assertion of Maire et al that such an analysis is useful as a cancer diagnostic (p.553, right col., last paragraph).

**Response to Remarks**

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the cited prior art. Applicants' arguments (p.9-15 of Remarks) have been fully and carefully considered but are not found to be persuasive.

Applicants have argued that Maire et al does not teach "mutation levels", however as set forth by in the rejection and consistent with the broadest reasonable interpretation of the limitations of the claims, the examiner maintains that the teaching of Maire et al teaches the association of the KRAS mutation with pancreatic cancer, thus detection in a particular sample of a 100% level of mutation (the presence of cancer) versus a 0% level of mutation (an indication of pancreatitis).

And while applicants have argued (p.11 of Remarks) that Maire et al teaches that using KRAS mutations as the only metric in a diagnostic may lack sensitivity, the argument is not persuasive in light of the teachings of Maire et al and the limitations of the claims. Maire et al teaches that a method comprising KRAS analysis with serum Ca 19.9 levels allows for 98% sensitivity. While Applicants argue that sensitivity and negative predictive value are limited in an assay that only looks at presence or absence

of KRAS mutations (p.11 of Remarks and p.13 of the Remarks), it is noted that the methods are 'comprising' the steps recited in the claims, and thus allow for the addition of any non-recited steps, where given the express teachings of Maire et al the skilled artisan would recognize that methods wherein the serum Ca 19.9 level is analyzed yield more accurate results. In the instant case there is no negative limitation in the claims, nor is there any basis for any negative limitation in the specification as originally filed, the would required that a serum Ca 19.9 levels may not be analyzed.

Applicants have argued that there is no motivation for the skilled artisan to use the methods of Schouten et al in the analysis of KRAS mutations as taught by Maire et al (p.12 of Remarks and p.14 of Remarks). The argument is not found to be persuasive because Schouten et al specifically teaches that the methods may be used for SNP mutation detection (p.11, left col.), where the mutations detected by Maire et al are single nucleotide mutations. And while the expectation of some advantage is one rationale for combining references, in the instant case at the very least the skilled artisan would recognize that the methods of Schouten et al would provide alternative methods for mutation analysis.

The rejection as set forth is **MAINTAINED.**

### ***New Claim Rejections - 35 USC § 103***

7. Claims 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schouten et al (2002), as cited on the IDS of 08/25/2006, in view of Maire et al

(2002) and Lecomte (2002), as previously applied to claims 6, 10-13 and 77-81, and further in view of Nazarenko et al (2002).

The teachings of Schouten et al in view of Maire et al and Lecomte are applied to claims 82 and 83 as they were previously applied to claims 82 and 83 as they were previously applied to claims 6, 10-13 and 77-81.

Schouten et al in view of Maire et al and Lecomte does not specifically provide for quantitative or real time amplification (claim 82) or multiplex amplification (claim 83). However, such methods were well known in the art at the time the invention was made and are taught by Nazarenko et al.

Nazarenko et al provides methods that include quantitative real time PCR in a multiplex format.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Nazarenko et al for the detection methods as rendered obvious by Schouten et al in view of Maire et al and Lecomte. The skilled artisan would have been motivated to us the methods of Nazarenko et al based on the teaching of Nazarenko et al that such methods are efficient, reliable, and cost-effective (p.2, left col.).

**Response to Remarks**

With regard to newly presented claims 82 and 83, Applicants have set forth (p.15 of Remarks) that Schouten et al specifically teaches against the use of qPCR, particularly multiplex qPCR. However, in reading the teachings of Schouten et al, the Examiner has concluded that any teaching away for the use of multiplex PCR is

mentioned in Schouten with specific regard to spectral overlap in dyes that may be used, where Schouten et al specifically mentions situations in which many different primer pairs may be requires (e.g. in the analysis of the 79 exons of the DMD gene). In the case of the instant claims there is no requirement where such a multitude of primer pairs are used, and Nazarenko et al clearly teaches success in using a multiplex format in a quantitative real time PCR technique.

## ***Conclusion***

8. No claim is allowed. No claim is free of the teachings of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Primary Examiner, Art Unit 1634